Complementary diversification of dendritic cells and innate lymphoid cells

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Abstract

Dendritic cells (DCs) are professional antigen presenting cells conventionally thought to mediate cellular adaptive immune responses. Recent studies have led to the recognition of a non-redundant role for DCs in orchestrating innate immune responses, and in particular, for DC subset-specific interactions with innate lymphoid cells (ILCs). Recently recognized as important effectors of early immune responses, ILCs develop into subsets which mirror the transcriptional and cytokine profile of their T cell subset counterparts. DC diversification into functional subsets provides for modules of pathogen sensing and cytokine production that direct pathogen-appropriate ILC and T cell responses. This review focuses on the recent advances in the understanding of DC development, and their function in orchestrating the innate immune modules.

Introduction

Dendritic cells (DCs) arise from the bone marrow (BM) and seed peripheral tissues and lymphoid organs [1]. Initially identified by their robust capacity for activating T cells, they are now recognized as modulators of both innate and adaptive responses [2]. Four different lineages can be classified as DCs: classical DCs (cDCs) [1], plasmacytoid DCs (pDCs) [3;4], monocyte derived DCs (moDCs) [5–7] and Langerhans cells [8]. cDCs are also heterogeneous, and can be divided into at least two major branches, but are likely more diverse [9]. In the mouse spleen, the two major cDC subpopulations are distinguished by expression of the surface markers CD8 α and CD172a (Sirp α), whereas in peripheral tissues, patterns of other markers such as CD103 and CD11b can be used to identify the splenic cDC subset equivalents [10;11*]. This review focuses on recent progress in the development and functional diversity of cDC subsets, and in particular their modes of orchestrating innate immune responses.

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DCs develop from distinct BM progenitors

The cellular stages involved in murine DC development, briefly described here, have been recently reviewed [12;13]. DCs originate in the BM from the common myeloid progenitor (CMP) [14]. The macrophage-DC progenitor (MDP) develops from the CMP and is restricted to cDC, pDC, macrophage and monocyte lineages [15;16]. Subsequently, a common DC progenitor (CDP) that expresses the macrophage colony-stimulating factor receptor (M-CSFR) and fms-related tyrosine kinase 3 (Flt3), but lower levels of stem cell factor (c-Kit) as compared to the MDP, has only pDC and cDC potential [17;18]. The pre-cDC, which develops from the CDP, exits from the BM and seeds lymphoid and peripheral tissues, where it differentiates into both cDC subsets [17;19]. Unlike cDCs, pDCs develop fully in the BM. Recently, segregation of DC progenitors based on M-CSFR expression has identified an M-CSFR-negative population that preferentially gives rise to pDCs [20*]. Immature pDCs in the BM can be identified as CD11c⁺B220⁺CCR9⁻Ly49Q⁻; upon maturation, pDCs acquire expression of CCR9 and Ly49Q and egress from the BM [21]. However, these pre-cDC and pDC progenitors, as currently defined, do not entirely exclude cDC and pDC potential, respectively [19;20*;22]. The splenic pre-cDC retains approximately 50% of the pDC potential relative to unfractionated BM [19], while the CCR9⁻ pDC progenitors can differentiate into CD11b⁺ cDCs upon granulocyte macrophage colony-stimulating factor (GM-CSF) stimulation [22]. Thus, further refinements in the definitions of these committed progenitors may be required before a mechanistic pathway of their development can emerge.

Cytokine regulation of DC homeostasis

DC development is dependent on the growth receptor Flt3 and its downstream transcription factor STAT3 [23–25]. Flt3 expression is maintained on DC progenitors and mature cDCs [26*], and loss of Flt3 signaling results in significantly reduced cDCs *in vivo* [27]. Treatment with Flt3 ligand (Flt3L) induces CDP proliferation and cDC expansion [27]. Other cytokines, such as GM-CSF, are also involved in DC homeostasis and loss of both GM-CSF and Flt3L has been shown to exacerbate DC deficiencies *in vivo* [28]. However, the exact function of GM-CSF in cDC homeostasis has been complicated by discordant observations [29;30]. One study has found that peripheral CD103⁺ cDCs develop normally in mice lacking GM-CSFR but are characterized by lower levels of CD103 expression relative to control mice [29]. In contrast, a subsequent study has suggested that loss of GM-CSF signaling reduces CD103⁺ cDCs in lung and CD103⁺CD11b⁺ cDCs in small intestine. However, in that study decreased CD103 expression has been interpreted to indicate the developmental failure of particular cDC peripheral populations in the absence of GM-CSF signaling [30].

Zbtb46 identifies cDCs committed progenitors

Zbtb46 is a transcription factor specifically expressed in cDCs within the immune system [31*;32*]. Analysis of BM from mice harboring a *Zbtb46*-GFP reporter allele found that progenitors expressing *Zbtb46* had lost potential for generation of pDCs and only develop into cDCs [31*]. However, the function of Zbtb46 in cDC development is not fully

understood. Overexpression of *Zbtb46* by retrovirus into unfractionated BM cells causes a bias in favor of the development of cDCs and against neutrophils *in vitro*; nonetheless, loss of *Zbtb46*, as assessed using homozygous *Zbtb46^{gfp/gfp}* mice, does not adversely impact neutrophil or augment cDC population frequencies [31*]. A role for *Zbtb46* as a transcriptional repressor in cDCs at steady state has been reported using an independent *Zbtb46^{-/-}* mouse strain [33]. Microarray analysis of *Zbtb46*-deficient cDCs shows an upregulation of more than 2,000 genes, based on a historical comparison to microarrays of wild type cDCs [33]. Further, loss of *Zbtb46* results in a partial activation phenotype of cDCs at steady state, in particular higher expression of MHC class II and co-stimulatory molecules [33]. However, similar results have not been reported with homozygous *Zbtb46^{gfp/gfp}* mice. *Zbtb46* may prove useful in allowing the further characterization of cDC progenitors, and understanding the pathways governing its expression could help identify the developmental stages of cDCs.

L-myc mediates cDC homeostasis *in vivo*

A recent study reported that L-myc (*MycII*), a c-Myc (*Myc*) and N-Myc paralogue, is specifically expressed in pDCs and cDCs [34]. c-Myc is highly expressed in progenitor cells and is required for proliferation and homeostasis [35], but in the murine DC lineage, *MycII* and not *Myc* is expressed from the CDP stage onwards and is maintained in cDCs outside the BM [34]. Treatment of cDCs with GM-CSF induces L-myc expression and loss of the latter results in a significant reduction in cDC proliferative capacity and cDC numbers in the lung [34], a tissue rich in GM-CSF [36]. Since loss of GM-CSFR also impairs cDC expansion [33], these findings suggest L-myc activity is required for GM-CSF induced proliferation. Functionally, *MycII^{-/-}* mice have a reduction in the extent of T cell priming during infection with the bacterial pathogen *Listeria monocytogenes* and vesicular stomatitis virus [34]. The reason for the switch from c-Myc to L-Myc expression during the development of DCs is still obscure, as it would seem that c-Myc should also be capable of supporting mitogenic activity downstream of GM-CSF. Possible reasons include constraints on c-Myc expression that might impair c-Myc levels during inflammation, or alternatively, different transcriptional targets of c-Myc and L-myc, issues that require further investigation.

Innate lymphoid cells mediate defense in response to distinct cDC subsets

Early studies on DC subsets have identified CD8 α ⁺ cDCs as specialized cross-presenting cells that induce CD8⁺ T cell responses in response to viral infections [37–42], while CD8 α -negative cDCs induce CD4⁺ T cell responses [43]. More recent studies, however, have highlighted the important roles cDC subsets play in modulating a vast array of immune responses, and in particular, their critical role in activating innate lymphoid cells (ILCs) by secretion of pro-inflammatory cytokines[44–46**;47**].

ILCs are lymphocytes lacking recombined antigen-recognition receptors that are dependent on the transcription factors ID2 and PLZF for their development [48–51**]. These populations of cells are involved in lymphoid organogenesis and tissue repair, as well as pathogen clearance [52–54]. Over several years, it has come to be recognized that ILCs develop into subsets, now classified as groups ILC1, ILC2, and ILC3 [55], that share a

substantial similarity in cytokine profiles and transcription factor dependence with CD4⁺ T cell subsets T_H1, T_H2 and T_H17, respectively [56]. ILC1s secrete high levels of interferon (IFN)- γ upon IL-12 stimulation and are dependent on Nfil3 (E4BP4), T-bet, Ets-1 and IL-15 for their development and function [57–64]. ILC2s secrete high levels of IL-4, IL-5 and IL-13 in response to parasitic helminths and allergen challenges [50;65–67] and are dependent on the transcription factors Gata3, Rora and Gfi1 [68–71]. ILC3s, which include lymphotoxin inducer (LTi) cells, CD4⁺ LTi-like cells, and NKp46⁺ cells, secrete high levels of IL-22 upon IL-23 stimulation and are dependent on ROR γ t and AHR [72–75]. Recent studies have shown a critical role for CD8 α ⁺ and CD11b⁺ cDCs as the obligate sources of inflammatory cytokines required for the activation of ILC1s and ILC3s, respectively [44;46**;47**].

Batf3-dependent CD8 α ⁺ cDCs support Type I immunity

The transcriptional regulation of CD8 α ⁺ cDCs has been studied extensively. CD8 α ⁺ cDC development is dependent on Irf8, ID2, Nfil3, Batf3 and Bcl-6 [76–81]. However, the developmental stages at which these transcription factors are required are still unclear. Irf8 is expressed in early progenitors, and loss of Irf8 impairs cDC and pDC development [76;77;82]. ID2 deficiency only affects CD8 α ⁺ cDCs and not pDCs, suggesting ID2 is involved in cDC development downstream of Irf8 [78]. *Nfil3*^{-/-} mice also have impaired CD8 α ⁺ cDC development, and *Nfil3*-deficient pre-cDCs have a two-fold decrease in Batf3 expression, suggesting Nfil3 acts upstream of Batf3 [79]; however, it is unclear if Batf3 is indeed a direct target of Nfil3. Finally, expression of Batf3 and Bcl-6 is not induced until later stages of CD8 α ⁺ cDC development [26;81]. CD8 α ⁺ cDC development, which is impaired by Batf3 deficiency, can be compensated by Irf8 interactions with Batf and Batf2 [83], which have the ability to interact with Irf8 in the same manner as Batf3 [84]. Importantly, the specific function for Batf3 in the development of CD8 α ⁺ cDCs is unclear; nonetheless, analysis of *Batf3*^{-/-} mice has provided ample insight into the critical role CD8 α ⁺ cDCs play in modulating innate responses.

The Batf3-dependent CD8 α ⁺ cDC is necessary for induction of type I responses to *Toxoplasma gondii* infection, based on their non-redundant secretion of IL-12, which is necessary for NK cell activation and concomitant production of IFN- γ (Fig. 1A) [44;45;85–88]. Recognition of *T. gondii* infection by the CD8 α ⁺ cDC requires appropriate TLR signaling, since loss of Myd88 in cDCs during parasite infection caused a significant reduction in IL-12 production resulting in impaired parasite clearance [45]. Recent studies have shown that cDC sensing of *T. gondii* is dependent on TLR11/TLR12, which recognize profilin, resulting in IL-12 production and parasite clearance [89*;90*]. The susceptibility of *Batf3*-deficient mice to this pathogen [44], therefore, demonstrates that a DC subset, previously considered non-redundant strictly in adaptive immune functions, plays a critical role in coordinating innate immune responses to a lethal pathogen.

Recently, examination of *Batf3*^{-/-} mice has revealed a role for CD8 α ⁺ cDCs in modulating invariant natural killer T cell (iNKT) responses. iNKTs express an invariant V α 14 chain and respond to glycolipid antigens, such as α -galactosylceramide (α -GalCer) [91] presented on CD1d molecules [92;93]. cDCs express CD1d and mediate iNKT negative selection in the

thymus [94]. Furthermore, cDCs upregulate co-stimulatory molecules and secrete IL-12 in response to treatment with α -GalCer [95;96] and DCs pulsed with such glycolipid prolong IFN- γ production by iNKT cells [97]. Further, iNKT responses are reduced in *Batf3*^{-/-} mice, suggesting that CD8 α ⁺ cDCs are the main regulator of iNKT activation [98*]. Nonetheless, the mechanism mediating this finding requires further analysis, as it is unclear if antigen presentation on CD1d molecules by CD8 α ⁺ cDCs is necessary for iNKT induction, or whether IL-12 secretion is sufficient for this process to occur.

Development and ontogeny of CD11b⁺ cDCs

The transcriptional networks regulating CD11b⁺ cDC development remain incompletely understood. Several transcription factors including Irf4, Notch2, and RelB, have been implicated in CD11b⁺ cDC development and homeostasis, however, a transcription factor that selectively controls development of CD11b⁺ cDCs remains unidentified. For some time, it was thought that Irf4 was required for this branch of cDCs [77]. Nonetheless, it is now it is recognized that *Irf4*^{-/-} mice retain CD11b⁺ cDCs, which fail to induce CD4 expression and to migrate to lymph nodes during immune responses [99*]. In peripheral tissues, *Irf4*^{-/-} mice have a two-fold decrease in CD103⁺ CD11b⁺ DCs in the small intestine lamina propria (SI-LP), and are completely absent in the mesenteric lymph node (MLN) [100*;101*]. Notch2 signaling is necessary for the development of ESAM⁺ CD11b⁺ splenic cDCs and CD103⁺ CD11b⁺ cDCs in the SI-LP, but this reduction is not observed in other tissues [102]. Non-canonical NF- κ B signaling is also involved in CD11b⁺ cDC homeostasis; loss of *Relb* [103;104], *Ltbr* [105], *Nik* or *Nfkb1* [47**] results in a partial reduction of splenic CD11b⁺ cDCs. However, the basis of these transcriptional requirements is still unclear. For example, the involvement of *Relb* in CD11b⁺ cDC development has been inferred from the decrease in the number of CD8 α -negative cDCs rather than loss of CD11b⁺ cDCs [104]. Conceivably, Irf4-expressing cDCs develop in the absence of RelB but fail to express a limited set of surface markers such as CD4.

The origins of SI-LP DCs have been elegantly shown in studies testing the developmental potential of DC progenitors by adoptively transferring MDPs, CDPs and pre-cDCs *in vivo*. All three progenitor populations are able to develop into CD103⁺ and CD103⁺CD11b⁺ cDCs in the SI-LP. Surprisingly, only the MDP gives rise to CD103⁻CD11b⁺ cDCs, suggesting that this population may originate from monocytes and not a DC committed progenitor [11*; 106*]. Analysis of *Zbtb46*-GFP mice has identified heterogeneous expression of *Zbtb46* in the CD11b⁺ CD103⁻F4/80⁻ DC population in the SI-LP [47**]. Partial deletion of that population is also observed in the diphtheria toxin (DT)-based cDC depletion model using *Zbtb46*-DT receptor (DTR) mice, suggesting a mixed contribution from multiple myeloid lineages to this population [107*]. It is possible that *Zbtb46*-expressing CD103⁻CD11b⁺ and CD103⁺ CD11b⁺ cDCs are developmentally related, and that expression of CD103 defines fully mature SI-LP CD11b⁺ cDCs. Alternatively, CD103⁻CD11b⁺ cDCs could be a separate lineage. In a murine model of DSS-induced colitis, Ly6C^{hi} monocytes can develop into moDCs in a model of DSS-induced colitis [108*]. During inflammation, colonic Ly6C^{hi} monocytes give rise to a CX3CR^{int}Ly6C^{lo} population which has a transcriptional profile similar to cDCs. Specifically, these cells express *Zbtb46* and *Flt3*, genes restricted in the periphery to cDCs. Functionally, these moDCs were able to migrate to lymphatic tissue,

process antigen and induce T cell proliferation [108*]. These findings provide evidence for the differentiation of monocytes into DCs during inflammation; however this phenomenon has not been analyzed at steady state. Analysis of reporter mice combined with lineage tracing could help identify monocyte contributions to CD11b⁺ DCs.

Notch2-dependent CD11b⁺ cDCs mediate pathogen-selective defenses in the intestine

The dependence of splenic CD8α⁺ and peripheral CD103⁺ cDCs on Batf3 for their development has helped to establish the functional restriction of this branch of cDCs in defense against intracellular pathogens [39;40;44;80;109]. In contrast, for Batf3-independent cDCs, some analysis using other genetic models indicates distinct functional specialization of CD11b⁺ cDC subsets. It was known that IL-23 and IL-22 production by innate cells is crucial during early stages of infection with *Citrobacter rodentium*, a mouse model for enteropathogenic *Escherichia coli* [110*–112]. Recent studies have identified CD11b⁺ cDCs as the non-redundant source of IL-23 in response to administration of bacterial flagellin [46**] and conditional deletion of Notch2 in cDCs has revealed that CD11b⁺ cDCs are required for clearance of *C. rodentium* by modulating the IL-23/IL-22 cytokine axis (Fig. 1B) [47**;107*]. Mixed chimera analysis indicated that the Notch2-dependent CD11b⁺ cDCs are the non-redundant critical source of IL-23 for resistance to *C. rodentium*; specifically, the susceptibility of *Notch2-deficient* mice to this pathogen appears to be due to failure of innate defense [47**]. Importantly *Irf4*^{-/-} and *Ccr7*^{-/-} mice, whose DCs exhibit a defect in migration [99*;113], do not show the same dramatic susceptibility to *C. rodentium* infection as mice lacking Notch2 in cDCs [47**]. This result suggests that IL-23 secretion by tissue resident CD11b⁺ cDCs is sufficient for inducing IL-22 production by ILC3s and, hence, effective local control of the pathogen.

IL-23 has also been implicated in the stabilization of Th17 commitment [114]. However, the non-redundant production of IL-23 by CD11b⁺ cDCs during infection with *C. rodentium* does not necessarily indicate that these cells are also involved in T_H17 polarization. Nevertheless, recent studies have shown a role for CD11b⁺ cDCs in T_H17 differentiation and function. Deletion of Notch2 in cDCs leads to a decrease in T_H17 numbers in the MLN [102], and loss of *Irf4* hinders the induction of T_H17 differentiation by small intestine CD103⁺CD11b⁺ cDCs [100*;101*]. These findings have been further corroborated by specific deletion of SI-LP CD103⁺CD11b⁺ cDCs using a human Langerin-DTA transgenic mouse model which also resulted in a decrease in T_H17 cell numbers [115]. However, further analysis is needed to resolve the role DCs play in T_H17 induction both at steady state and during infection. It has been recognized that other cytokines such as IL-6 and TGF-β, but not IL-23, are required for polarization of T_H17 cells from naïve T cells [116;117]. Further, secretion of IL-22 by CD4⁺ T cells can occur independently of IL-23 [118]. These results suggest that CD11b⁺ cDCs may be dispensable for initial differentiation of T_H17, but instead may enhance T_H17 commitment and cytokine production via secretion of IL-23 [119; 120].

Although significant progress has been made in understanding the immune responses necessary for clearance of enteropathogenic bacteria, several aspects are still unclear. The physiological stimuli required for IL-23 secretion by cDCs are not understood. For example, it is unknown whether *C. rodentium* directly activates cDCs or if secondary signaling induces IL-23 production in cDCs. Although flagellin can induce IL-23 secretion by CD11b⁺ DCs, *C. rodentium* is an aflagellate organism and should not stimulate cDCs via TLR5 [121]. Infection with a flagellate organism such as *Salmonella typhimurium* could provide insight on the mechanisms regulating IL-23 secretion by CD11b⁺ DCs. Further, it is unclear if the CD103⁺ or the CD103-negative CD11b⁺ cDC populations in the SI-LP are sufficient for clearance of *C. rodentium*. Although loss of Notch2 severely diminishes SI-LP CD103⁺ CD11b⁺ DCs, this deficiency could also impair CD103⁻CD11b⁺ cDC function [115]. Finally, other aspects of IL-23 signaling in addition to IL-22 induction have not been studied. Mortality and severity of disease during infection by *C. rodentium* is more severe in *Il23a*^{-/-} mice when compared to *Il22*^{-/-} mice [110*,118], further examination of the effects of IL-23 on other cells could provide insight on the pleiotropic functions of this cytokine.

CD11b⁺ cDCs mediate type II immunity

The specific secretion of IL-12 and IL-23 by CD8α- and CD11b-expressing cDCs, respectively, suggests that a specific DC subset that regulates type II immunity may exist. Depletion of CD11c⁺ expressing cells in *Itgax-DTR* mice significantly impairs T_H2 responses against the parasitic helminth *Schistosoma mansoni* [122]. Recent studies suggest that the CD11b⁺ cDC subsets may modulate type II responses. A CD11b⁺ cDC subset expressing FCεR1 initiates *in vivo* type II immune responses to immunization with house dust mite (HDM) antigen [123]. In addition, both CD11b⁺ cDCs and moDCs are rapidly recruited to lung airways upon HDM challenge, yet only CD11b⁺ cDCs are able to migrate to the lymph node and trigger T_H2 responses [124*]. Nevertheless, moDCs are sufficient to induce T_H2 responses in *Flt3l*^{-/-} mice immunized with a high dose of HDM antigen [125*]. Recently, it has been shown that loss of *Irf4* in CD11c⁺ cells impairs T_H2 responses in a model of allergy based on HDM antigen immunization [126]. Further, using *Irf4*^{-/-} mice, two recent studies have identified a subset of dermal cDCs expressing CD301b and PDL2 that mediate T_H2 responses during allergic responses or infection with *Nippostrongylus brasiliensis* [127;128]. However, these studies did not address a possible defect in DC migration from tissues to lymph nodes due to *Irf4* deficiency [99*]. It is possible that reduced T_H2 responses in these studies [127;128] result from impaired cDC migration to lymph nodes rather than a selective *Irf4* involvement in T_H2 priming. Also, it is unclear if *Irf4*-expressing CD11b⁺ cDCs are a uniform group [9]. Finally, the involvement of CD11b⁺ cDCs in modulating innate type II responses is unstudied.

Concluding remarks

At present, two cDC subsets have been examined with respect to their specialization in providing defense against different types of pathogens. The Batf3-dependent subset of cDCs, which is characterized by high levels of *Irf8*, appear specialized in priming CTL responses against many viruses and for promoting type I defense against intracellular pathogens, such as *T. gondii*. This latter function is not restricted to priming T_H1 responses, but also

enhancing innate defenses that involve early production of IFN- γ produced by innate lymphocytes such as ILC1 or NK cells [44;45]. Notch2-dependent subsets of CD11b⁺ cDCs have been shown to specialize in defense against one pathogen, *C. rodentium*, but are dispensable for defense against pathogens such as *T. gondii* and *L. monocytogenes*. Thus, in both cases, specialized DC subsets appear to engage innate immune cells in a manner that is not simply an adjuvant to defense, but critical for resistance. An unresolved issue is how the different subsets manage to acquire their specialized functions. To some degree, the particular expression patterns of innate molecular sensors and the capacity for specific cytokine production may be involved, although the molecular basis for these have not been well worked out.

Different sensing and effector capacities exhibited by distinct cDC subsets can provide a system to drive activation of pathogen-appropriate ILC subsets, as is the development of pathogen-appropriate CD4⁺ T cell subsets. The similarity in transcriptional features underlying ILC and T cell diversity [56] might suggest that the latter was adapted during evolution from the former, and that both effectors arms rest on the same platform of DC diversity. If ILCs evolved before T cells, then cDC subsets may have first developed to link particular pathogen sensors with the production of cytokines needed to activate pathogen-appropriate ILC subsets. Later, with the introduction of RAG-dependent adaptive immunity, this established DC subset program would acquire the capacity for antigen presentation in addition to the pre-existing cytokine circuitry. CD4⁺ T cells would adapt to the use of these same cytokines to trigger their development down the transcriptional pathways first established in ILCs. Testing this speculation may be difficult, since the ancestral species representative of this transition may no longer exist.

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Highlights

- Transcriptional requirements of DC subset development.
- Batf3-dependent CD8 α^+ DCs mediate type I immune responses.
- CD11b $^+$ DCs orchestrate ILC3 and T_H17 responses.

Figure 1. Dendritic cells orchestrate pathogen-appropriate innate and adaptive immune responses

(a and b) A pre-cDC progenitor develops into both the Batf3-dependent $CD8\alpha^+$ cDC and the Notch2-dependent $CD11b^+$ cDC subsets. **(a)** $CD8\alpha^+$ cDCs respond to *Toxoplasma gondii* infection by sensing the antigen profilin via TLRs 11/12. Activated $CD8\alpha^+$ cDCs secrete IL-12 which induces IFN- γ secretion by ILC1/NK cells. IFN- γ activates infected cells, such as M Φ 's, to produce nitric oxide and reactive oxygen species, which are necessary for parasite control. In parallel, activated $CD8\alpha^+$ cDCs migrate to lymph nodes and promote differentiation of T_H1 cells, which enhance parasite clearance. **(b)** Infection with *Citrobacter rodentium* activates $CD11b^+$ cDCs in the small intestine by an unknown mechanism. Upon activation, tissue resident $CD11b^+$ cDCs produce high levels of IL-23 which induces IL-22 production in R γ dependent ILC3s and possibly acts on other cells as well. IL-22 activates the epithelial layer to secrete the bactericidal lectin RegIII γ , which is necessary for *C. rodentium* clearance. $CD11b^+$ cDCs also migrate to the mesenteric lymph node where they induce T cell differentiation into T_H17 and T_H22 cells. These effector T cells migrate back to the site of infection and are the adaptive source of IL-22. cDC: classical dendritic cell. TLR: Toll-like Receptor. ILC3: Innate lymphoid cell type 3. IFN- γ : Interferon- γ . M Φ : Macrophage